In superb initial chapters, pathways involved in growth factor receptor signaling in hematopoietic cells are discussed, including JAK/STAT, Ras, phospholipase C, and recently described inhibitory pathways. Also, the transcriptional regulation of genes required for hematopoietic cell differentiation, such as SCL, GATA, and AML-1, is reviewed. Increasingly, as in other cell systems, cell adhesion is becoming appreciated as playing a role in signaling (not only localization) in hematopoietic cells; this topic is covered in several additional chapters. Conceptually, these chapters build a foundation for understanding both future targets of molecular interventions and the microenvironment requirements for large-scale manipulations of hematopoietic cell products.

Over the last 30 years there has been a significant increase in the use of bone marrow transplantation for the treatment of malignant, genetic, and in some cases autoimmune diseases. Increasingly, bone marrow cells are being replaced with mobilized peripheral blood or umbilical cord blood as sources of transplantable stem cells. The use of allogeneic, autologous, and cord blood transplants is reviewed in helpful middle chapters. The authors have done, with rare exceptions, a nice job of summarizing the use, advantages, and disadvantages of each of these approaches in current therapies. In so doing, the chapters provide a brief overview of increasingly complex data from multiple sources with respect to outcomes and complications. Two noticeable oversights are the lack of discussion of the emerging use of haploidentical (usually parenteral or sibling) transplants in the treatment of malignant disesase and the use of so-called "mini" or submyeloablative transplants, which may have an enormous impact on the future treatment of nonmalignant diseases.

Cellular adoptive immunotherapy entails the transfer of effector cells of the immune system, usually CD4 or CD8 lymphocytes for the treatment of malignant diseases or infections. Remarkable progress has been made in this area, including development of effective adoptive transfer methods to treat leukemia, Epstein-Barr virus (EBV)-associated lymphoma and melanoma. Additional applications include treatment of serious, often fatal, EBV and cytomegalovirus infections in the immunocompromised host. In another excellent chapter, the basic biology of lymphocyte-mediated immunity is discussed, and this and other clinical applications are reviewed, including data on ongoing clinical trials. Future applications in human immunodeficiency virus (HIV) treatment are considered in light of the ability of natural-host T cell response to only partially control HIV virus replication. Such future applications may well require genetic modification of T lymphocytes. Ex vivo expanded dendritic cells may also prove useful in future therapies.

Success of cellular and gene therapies in the clinical setting will require translating laboratory-based methods into cell production and modification processes in large scale with standards of safety similar to other therapeutics. In the latter chapters of this book, the editors have attempted to compile several chapters reviewing core technologies required for clinical applications of ex vivo cell therapies. These technologies include cell separation, cell expansion, and gene modification. The goals of cell separation include selection for "target cells" and passive elimination of contaminating tumor or effector cells. Cell separation, by purifying a rare target cell population, provides the added benefit of reducing the amount of reagents and simplifying manipulations (and therefore potential complications) required for downstream processes. The goals of cell expansion include both manipulating the cellular constituents of the final cell product and facilitation of transplants using a limited initial number of cells. Clearly the efficacy of these emerging technologies is yet to be shown in the clinic. The regulatory aspects of cell purification and expansion technology are discussed. Commercial systems of cell purification and cell expansion are covered, although this information is derived from scientists at only two biotechnology companies while several other relevant proprietary approaches are not discussed.

Gene delivery technology, including virus vectors, liposome, particle-mediated, electroporation, and direct DNA injection are reviewed. To accomplish this in limited space required a brief treatment of each technology covering basics without significant details. Advantages and disadvantages of each technology are noted providing a useful guideline to those not currently in the field. No discussion of regulatory issues as these relate to human gene therapy trials is present. Workers in the field will recognize that these regulations are significant in both volume and detail, but their inclusion at least in summary form would have added to the overall usefulness of this book.

Understanding the molecular processes that control cell growth and differentiation is a major goal of cell and molecular biologists. Application of this knowledge to defining the molecular defects causing human diseases has been the task of scientists in the past 20 years, beginning with the characterization of the molecular basis of hemoglobinopathies. Over the next several decades the development of strategies to repair the cellular systems affected by genetic mutations will be an ongoing goal. This book provides a compact review of the basic biology of hematopoiesis and technologies being developed to manipulate hematopoietic cells either to eliminate diseased cells or to restore and augment normal function to the blood system.

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Prokaryotic Genomes: The Hidden Code

Organization of the Prokaryotic Genome
Edited by Robert L. Charlebois
Washington, D.C.: ASM Press (1999). 394 pp. $79.95

It is evident that biology has entered a new period, sometimes called the genomics era. Genomic technologies

involve efficient, high-throughput data collection and analysis; improved methodologies and technologies have allowed the generation of unprecedented quantities of biological information in the form of nucleotide sequence from a wide variety of species. The availability of whole genome sequence data has, in turn, allowed other areas of functional genomics to accelerate. Whole genome RNA and protein expression studies and protein–protein interactions maps, catalogs of essential genes, and the identification of genes required for establishment of disease are being realized as a result of genomic approaches. Whole genome sequencing is in full stride and holds the enormous promise of revolutionizing the way biological questions will be framed and greatly increasing the rate at which we will understand the function of genes and genomes.

To what extent has this promise been delivered? On many levels our ability to interpret and comprehend the nature of the genetic code is an ongoing process almost certainly in its infancy. In support of this statement is the uniform fact that at least one-third of each microbial genome sequence completed to date is composed of genes for which no functional prediction can be made. Beyond this issue is the notion that coding potential in genomes is likely to go well beyond the code used to translate nucleic acid sequence information into amino acid sequence. In this regard, it is harder to be quantitative about the extent of our current ignorance since, in many instances, we don't yet even clearly understand the relevant questions to ask. The book, *Organization of the Prokaryotic Genome*, describes both the computational and experimental tools being applied to genomics. While this aspect of the text is not novel, it is a necessary background to complement the more unique and exciting aspects that examine the available data in various areas of microbial biology to assess to what extent, beyond the combined function of individual genes, a genome is truly defined. This book may provide the thoughtful reader a new way to view the marvelously adaptive abilities of the microbes on this planet.

The first section of the book is focused on tools required for production of raw sequence data and assembly of that sequence into a complete genome. This is followed by a description of methods used to identify open reading frames (ORFs) and translation start sites. Strategies for genome sequencing include total-genome shotgun sequencing, primer walking sequencing, and a mixed strategy based on both approaches. Total genome sequencing is mainly suitable for the large genome centers that possess the infrastructure to generate the massive numbers of sequence reads together with the computational power necessary to assemble the random sequences generated. The directed-sequencing strategy is dependent upon ordered libraries of clones and good physical maps of the genome. This approach has been used in the yeast genome-sequencing project and is most appropriate for small genome centers with more limited sequencing capabilities. Experience has shown that the best overall strategy is a mixed approach combining the high-throughput random genome sequencing together with directed sequencing to close those gaps inevitably remaining after the random genome libraries have been sequenced and assembled. The book's evaluations of current sequencing and robotic technologies, primer synthesis, and software developments are especially relevant for investigators who are establishing or upgrading existing sequencing labs.

Subsequent scanning of the assembled genome for ORFs is a prerequisite for gene identification and functional genome analysis. An extensive discussion by a leading group in computational genomics summarizes current algorithms used for identification of ORFs and translation start sites. This group has written a suite of algorithms (called GeneMark) and therefore, much of the discussion is focused on this software. While the mathematical description of GeneMark (and Hidden Markov Model architecture) in general is complex, the reader is left with a good sense of their use, strengths, and shortcomings. One disappointing aspect of this chapter is the passing reference to other gene-finding programs and lack of a more complete comparison of other algorithms.

One particularly interesting chapter explores chromosome size, number, organization, topology, and the tools used for physical mapping of prokaryotic genomes. These tools include the commonly used pulsed-field gel electrophoresis (PFGE), optical mapping, hybridization techniques for clone linking analysis, and use of intron-encoded nucleases (such as CeuI), which uniquely cleave ribosomal genes and allow for subsequent differentiation of chromosomal DNA from plasmid DNA. With an increasing number of complete genome sequences and subsequent detailed restriction maps, one must question whether or not physical mapping of prokaryotic genomes remains a useful tool for genome analysis. However, given the ease and the low cost with which physical mapping can be done, investigators will most likely continue to use it as an effective genomics tool. Despite its shortcomings, one especially powerful use of physical mapping is as a means of performing comparative genomics to compare sequenced genomes with those related isolates that have not been sequenced. This approach will be especially useful when comparing genomes of related isolates of prokaryotic pathogens with known and well-documented virulence potentials. Perhaps, the most useful information is a table in which physical details of many bacterial genomes have been collected. Because much of this information is difficult to find, this table is a very useful resource. Finally, there is an intriguing discussion of organisms possessing multiple chromosomes, and of linear and circular replicons coexisting in the same bacteria. As more prokaryotic genomes are being sequenced, their dynamic nature and flexibility is becoming more apparent. Several bacteria have harbored multiple chromosomes that appear to exist in a dynamic flux between plasmid and chromosomal DNA. While the function of multiple chromosomes remains in question, there is an intriguing model introduced that suggests the *Escherichia coli* F-prime factor was the original prototype for the second bacterial chromosome.

The next section of this book is devoted to classification of prokaryotic genes and analysis of gene families. Prior to complete genome sequencing, prokaryotes were classified on the basis of G+C content and 16S rRNA-based grouping. With an increasing number of complete genome sequences, prokaryotes are now

classified on the basis several genome characteristics; including all encoded genes, genome organization, codon usage, ORF density, operon structure, and biosynthetic pathways. Several methods and databases have been developed that use these characteristics to classify prokaryotes and facilitate comparisons of shared genes and gene families. One example of such a database is COG (clusters of orthologous groups), which has been used to identify the closest homologs for each protein among all of the sequenced prokaryotes. Using these tools, a comparison of metabolic pathways and prokaryotic lifestyles may enable us to determine what changes in genome content and organization are required for adaptation to symbiotic, parasitic, or saprophytic growth. As more prokaryotic pathogens are sequenced, we can expect these approaches to produce insights into the unique metabolic properties of each type of pathogen. One outcome of this work is the developing need for actual experimental work to verify gene and gene family assignments. As with ORF finding, comparison databases and software is an evolving field with continual development of new tools.

Three chapters present a group of mechanisms involved in generation of chromosome rearrangement and maintenance of chromosome structure. These include homologous recombination, illegitimate recombination, and insertion (IS) elements and transposons. In response to changing environmental conditions or other stimuli, these mechanisms likely function cooperatively to remodel the chromosome and ensure continuing survival. It is therefore reasonable to view the prokaryotic chromosome as a collection of genes and operons in a selected order and orientation.

Three consecutive chapters deal with aspects of DNA topology and the seldomly covered subject of the nucleoid. These chapters draw attention to clear examples depicting instances where DNA supercoiling and gene positioning within a genome effects gene regulation. Additionally, a good description of the less clear role of the nucleoid and the partitioning of large 50 kb segments of DNA into discrete domains is put forward. This presentation typifies the general tone of the book in that there are many well-understood features of DNA that impart regulatory capabilities to an organism. These well-defined functions may, however, be greatly outnumbered by the number of features that we do not understand or have yet to recognize.

The next section of the book covers various aspects of genome stability, highlighting the seemingly enormous stability in terms of conservation of gene order (synteny) and genome content observed when one compares the genomes of the *Salmonella* species to the *Escherichia coli* K-12 genome. This fact is especially intriguing given the 120 million or so years since these bacteria diverged from a common ancestor. This high level of genome conservation is in stark contrast to that observed in the genomes of *Streptomyces* species, where enormous variability in genome size and gene arrangement occurs among various isolates. These contrasting examples highlight one of the greatest lessons of microbial sequencing and comparative genomics—generalizations based on a single model can be dangerous.

These chapters are appropriately followed by an excellent discussion of the general principles and parameters that promote and constrain genomic flux. Once again, the knowledge of whole genome sequences has allowed a direct assessment of the frequency and extent that microbes use various strategies to generate diversity in populations. The forces that drive genome evolution are perhaps for the first time being documented in clear and meaningful ways. The clear descriptions of the concepts that relate mechanisms of gene acquisition and gene loss in genome evolution and its relationship to cellular fitness complement the preceding section and the book in a very interesting and useful manner.

The book concludes with three chapters that describe disciplines and technologies that somewhat uniquely define the niche of genomics research. The first of these chapters expertly describes the computational aspects of genome analysis with an emphasis on what we can hope to learn about genome evolution and gene function. This is followed by a chapter detailing the current state of the art of proteomics. This chapter makes the important point that genomics and proteomics are very complementary and, to a large extent, mutually dependent. The final chapter describes various "genomic" approaches in use in various model organisms. This concluding chapter excites the reader by highlighting the enormous power of genomics and its ability to generate huge volumes of biological data.

In summary, we would recommend this book to anyone interested in prokaryotic genomics. With a few exceptions, the chapters are well written and informative. However, because the focus of several chapters was solely on *E. coli*, some of the discussions did not include relevant information for equally important prokaryotes, such as *Bacillus subtilis*. While it is true that there has been decades of work on *E. coli*, the genome sequences of many other bacteria, including *B. subtilis*, have been completed. With the completion of these sequences and as more basic experimental work is done, we hope that discussions such as those presented in this book will expand to include other prokaryotes.

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Data, Data Everywhere . . .

Genetics Databases
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Biological research is now significantly influenced by the burgeoning amount of genomics data available on the internet. *Genetics Databases* describes some of the more important sources of this information and explains some of the underlying principles behind the commonly used bioinformatics tools. The book is not aimed at the specialist computational biologist and assumes little knowledge. Each chapter is independent of the others, making the book ideal for reference, and the topics chosen for review include many areas of current interest. As such it will make an ideal resource for the many